REMARKS

Undersigned counsel for Applicants thanks Examiners Ton and Falk for extending the courtesy of a personal interview held on January 19, 2006 to discuss the outstanding Office Action and the contents of this Response. More specifically, characteristics of the hepatic progenitor cells were discussed.

Status of the Claims

Claims 1, 14, 27-37 and 40-55 were pending in this application. (Applicants respectfully note that the pending claims were inaccurately identified as 1, 14 and 27-55 in the Office Action Summary.) With this Response, claims 1, 14, 27, 28, 29, 42 and 49 have been amended; claim 40 has been canceled; and no new claims have been added. Upon entry of these amendments, therefore, claims 1, 14, 27-37 and 41-55 will be pending and under active consideration.

Applicants respectfully request entry of the amendments and remarks made herein into the prosecution history of the present invention. Reconsideration and withdrawal of the rejections set forth in the above-identified Office Action is respectfully requested.

Support for Claim Amendments

Claims 1, 14, 27-29, 42 and 49 have been amended. Support for bipotent hepatic progenitors which "exhibit at least one of the following characteristics: (1) expression of at least one of CD44H, alpha-fetoprotein, albumin or CK19, or (2) dull expression of a nonclassical MHC class Ia antigen, or (3) higher side scatter (SSC) relative to non-parenchymal cells as measured in a flow cytometer" may be found throughout the specification, and more specifically, at least summarized in the flowchart under section 6.11. Support for hepatic progenitors that have the capacity to differentiate "into hepatocytes or biliary cells" may also be found throughout the originally filed specification and claims and at least at page 10, lines 27-8.

Hence, Applicants submit that no new matter has been added by this amendment. Reconsideration and allowance of all the claims is respectfully requested.

Examiner's Response to Arguments

Applicants wish to thank the Examiner for withdrawing the rejections under 35 U.S.C. § 102. Applicants further thank the Examiner for withdrawing the obviousness-type double patenting rejections over claims in co-pending application nos. 10/358,325 and 10/135,700 in view of the Terminal Disclaimers filed.

Claim Rejections under 35 U.S.C. § 112, first paragraph

Enablement

Claims 1, 14 and 27-55 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to enable one of ordinary skill in the art to make and/or use the invention. In brief, the Examiner maintains that the expression of ICAM and lack of MHC class I are insufficient to uniquely identify the claimed bipotent hepatic progenitors. In support the Examiner states that "[t]he flow chart [of Example 6.11, paragraph 0079] has more steps than ... merely sorting the cells by two markers ... ." Applicants respectfully traverse this rejection on the following grounds.

At the outset, Applicants respectfully submit that the description of "additional" *method* steps to isolate a product does not suggest that those steps (*e.g.*, selection based on cell surface markers) are in any way necessary to uniquely identify the *product*. In other words, methods of isolation may include steps that are not necessary to uniquely arrive at the product, but which are nonetheless performed for practical considerations (*e.g.*, efficiency). By way of example, the Office Action correctly notes that a step to eliminate red blood cells is disclosed in the flowchart. However, this step is a practical consideration to merely expedite selection, but inclusion of the step does not imply that selection based on red blood cell markers is *necessary* to identify hepatic bipotent progenitors. In fact, it is not.

However, in order to move the instant application to allowance, Applicants have amended the independent claims to recite at least one of the following characteristics of the claimed hepatic bipotent progenitor cells: (1) expression of at least one of CD44H, alpha-fetoprotein, albumin or CK19, or (2) dull expression of a nonclassical MHC class Ia antigen, or (3) higher side scatter (SSC) relative to non-parenchymal cells as measured in a flow cytomerter. Further, at the Examiner's suggestion, the independent claims now explicitly recite bipotent

hepatic progenitors having the capacity to differentiate "into hepatocytes or biliary cells." In light of these amendments, Applicants submit respectfully that the pending claims are sufficiently enabled by the disclosure.

Applicants respectfully maintain that identification of cells based on the expression of at least one ICAM antigen and lack of MHC class Ia antigen expression in conjunction with an additional recited characteristic (*i.e.*, step (c) in claims 1, 27, 29 and 49) is indeed sufficient to uniquely identify the claimed bipotent hepatic progenitors. Example 6.4 provides evidence to substantiate that hepatic cell suspensions stained with anti-RT1A—specific for MHC class Ia—and anti-ICAM-1 could be sorted into discrete cell populations identifiable according to their respective staining pattern. *See, also*, Figure 4. These discrete populations were then screened to demonstrate that indeed the $ICAM^{+}RT1A^{-}$ population represented the bipotent hepatic progenitor cell population. Thus, Applicants respectfully submit that the instant claimed invention is sufficient to identify bipotent hepatic progenitor cells and enable one of ordinary skill in the art to accomplish same.

For at least these reasons, Applicants submit respectfully that the claims, as amended, meet the enablement requirement. Applicants solicit respectfully that the 35 U.S.C. § 112, first paragraph, rejection of the pending claims be thus withdrawn.

Written description

Claims 1, 14 and 27-55 stand rejected under 35 U.S.C. § 112, first paragraph, for also allegedly failing to describe the claimed subject matter in such a way as to reasonably convey to one of ordinary skill in the art that the inventors had possession of the claimed invention at the time the application was filed. In short, the Office Action states that "[t]here is no specific description of a cell with expression of ICAM and lack of MHC class Ia as a bipotent hepatic progenitor cell... ." Rather, it is alleged that "it is clear from [Example 6.4] that the cells are firstly stained for ICAM and MHC class Ia expression, and then further sorted in order to identify which fraction contains the claimed cell populations." Applicants respectfully traverse this rejection.

Applicants, first, wish to respectfully clarify the Examiner's interpretation of the procedure in Example 6.4. The Office Action correctly finds that liver cells were first stained with ICAM and RT1A. This step provides *four* distinct populations (*i.e.*, $ICAM^{+}RT1A^{+}$,

$ICAM^+RT1A^-$, $ICAM^-RT1A^+$ and $ICAM^-RT1A^-$). Rather than "restoring", however, these discrete populations were then assayed for indicia of bipotent progenitor status. In this way, the $ICAM^+RT1A^-$ population was identified as comprising bipotent hepatic progenitors, and the ICAM and RT1A markers were determined sufficient to uniquely identify this population.

Nonetheless, in order to move the instant application to allowance, Applicants have amended the claims to bipotent hepatic progenitors having expression of at least one ICAM antigen and lack of MHC class Ia antigen expression *in conjunction with* an additional recited characteristic (*i.e.*, step (c) in claims 1, 27, 29 and 49). The evidence in Examples 6.4 and 6.6 was discussed in detail in a previous Response and need not be repeated here. However, it is appropriate to kindly stress again that the claimed subject matter was later published in the peer-reviewed journal PNAS.[1] Given the additional fact that the PNAS publication stands as one of the most cited publications from the inventors' laboratory[2] and has never been repudiated by any laboratory to date further, substantiates that the invention was sufficiently enabled and described for one of ordinary skill in the art to practice the invention and appreciate that the claimed invention was in possession of the inventors.

Taken together, Applicants respectfully submit that the instant claimed invention is adequately enabled and described under 35 U.S.C. § 112, first paragraph. Accordingly, Applicants hereby kindly solicit withdrawal of same rejections.

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[1] Kubota H, Reid LM, "Clonogenic hepatoblasts, common precursors for hepatocytic and biliary lineages, are lacking classical major histocompatibility complex class I antigen," *Proc Natl Acad Sci U S A*. 2000 Oct. 24; 97(22):12132-7.

[2] Indeed, over 60 papers in the last two years have referenced the PNAS paper according to ISI Web of Science (citation index). Austin T and Lagasse E, "Hepatic regeneration from hematopoietic stem cells," Mech Dev 2003; 120:131-5 is an example.

CONCLUSION

Applicants submit that the application is in condition for allowance. Favorable reconsideration, withdrawal of the rejections set forth in the above-noted Office Action, and an early Notice of Allowance are requested.

Applicants' undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 295-4621. All correspondence should be directed to our address given below.

Respectfully submitted,

February 24, 2006
Date

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